UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

012316

DATE: September 18, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: NALED - *FQPA REQUIREMENT* - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 9/18/97
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel 9/18/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Karen Whitby
Chief, Risk Characterization & Analysis Branch, Health Effects Division (7509C)

BACKGROUND: On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Naled with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Naled as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
LAN storage

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Naled with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Naled as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS: Evaluation of the toxicology data base indicated the following:

1. Neurotoxicity

- In an acute delayed neurotoxicity study in hens, a single oral dose of Naled at 42 mg/kg to hens, resulted in mortality (4/40), clinical signs of neurotoxicity ("subdued", unsteady), and inhibition of brain cholinesterase activity (50%). Axonal degeneration of the spinal cord was increased in treated hens when compared to concurrent and historical controls. Although Naled did not cause frank neurotoxicity, a degenerative neuronal effect was manifested in the spinal cord. Naled did not cause inhibition of neurotoxic esterase (MRID Nos. 41630701).

- No treatment-related pathological lesions of the central or peripheral nervous systems were seen in an acute neurotoxicity study in rats following single oral doses of Naled at 0, 25, 100 or 400 mg/kg/day or in a subchronic neurotoxicity study in rats following dietary administration at 0, 0.4, 2 or 10 mg/kg/day for 90 days. In the acute study, in males the NOEL was 25 mg/kg/day and the LOEL was 100 mg/kg/day based on effects in the functional observation battery. In females, the NOEL was 5 mg/kg/day and the LOEL was 25 mg/kg/day based on minimal neurological compromise. In the subchronic study, for males, the NOEL was 10 mg/kg/day (HDT); a LOEL was not established. For females, the NOEL was 2 mg/kg/day and the LOEL was 10 mg/kg/day based on transient tremors (MRID Nos. 42861301 and 43223901).

2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Naled and comparable NOELs were established for adults and offspring.

- In a developmental toxicity study pregnant Sprague-Dawley rats received oral doses of Naled at 0, 2, 10 or 40 mg/kg/day during gestation days 6 through 19. For maternal toxicity, the NOEL was 10 mg/kg/day and the LOEL was 40 mg/kg/day based on clinical signs of neurotoxicity (tremors, hypoactivity, discharge from mouth and eyes, and dyspnea). For developmental toxicity, the NOEL was 40 mg/kg/day (HDT); a LOEL was not established (MRID No. 00138682 and 00144026).
- In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of Naled at 0, 0.2, 2 or 8 mg/kg/day during gestation days 7 through 19. No maternal or developmental toxicity was seen. Although the highest dose tested (8 mg/kg/day) did not induce maternal toxicity, the dose selection was supported by the results of a range-finding study. In the range-finding study, following oral dosing at 0, 2, 10 or 20 mg/kg/day during gestation, there was maternal mortality at 20 mg/kg/day and marked cholinergic signs at 10 or 20 mg/kg/day. The clinical signs observed in does at 10 mg/kg/day indicated that the highest dose tested (8 mg/kg/day) in the definitive study was adequate to assess the developmental toxicity potential of Naled. Based on these results, for maternal and developmental toxicity the NOEL was 8 mg/kg/day (HDT); a LOEL was not established (MRID No. 00146496).

3. Reproductive Toxicity

- In a two-generation reproduction study, when administered *via* gavage at 0, 2, 6, or 18 mg/kg/day to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 6 mg/kg/day and the LOEL was 18 mg/kg/day based on decreased body weight gains in F_O and F_1 males. For reproductive toxicity, the NOEL was 18 mg/kg/day (HDT); a LOEL was not established (MRID No.00146498).

4. Cholinesterase Inhibition

- No data are available to ascertain the effects of Naled on cholinesterase activity. ChE activity was not measured in the acute and subchronic neurotoxicity studies or in the adults and offspring either in the developmental (rats and rabbits) or the reproductive toxicity studies. Therefore, no comparisons could be made for this endpoint between adults and offspring.

5. Data Gaps

- The Committee determined that a 28 or 90-day neurotoxicity study in hens (Guideline §82-5) is required because of the neuropathological effects seen in the acute delayed neurotoxicity study.

- The Committee also decided to place the requirement for a developmental neurotoxicity study in rats in *reserve status* until submission and review of the 28/90-day neurotoxicity study in hens (Guideline §82-5).

6. Reference Dose (RfD)

- An RfD of 0.002 mg/kg/day was derived from the NOEL of 0.2 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on brain ChEI observed at 2.0 mg/kg/day in rats in a 2-year study. The UF of 100 included a 10 for intra-species and 10 for inter-species variation. This NOEL was supported by the 1-year study in dogs in which the NOEL of 0.2 mg/kg/day was based on ChEI and systemic toxicity.

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on mild cholinergic signs and decreases in plasma and brain cholinesterase activity at 10 mg/kg/day (LOEL) in rats.. The NOEL was 1 mg/kg/day.

Therefore, for acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained.. A Margin of Exposure of 1000 is required** to ensure protection of this population from acute (single) exposure to Naled for reasons stated below:

(i) A single oral dose in hens caused deaths, clinical signs indicative of neurotoxicity, inhibition of brain cholinesterase activity and histopathological lesions in the spinal cord.

(ii) Lack of evaluation of a critical endpoint (i.e., cholinesterase measurement) in the acute and subchronic neurotoxicity studies

(iii) Concern for the occurrence of developmental (fetal) effects following an acute *in utero* exposure in developmental toxicity studies.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on the brain cholinesterase inhibition observed at 0.2 mg/kg/day (NOEL) in a two year rat study. The LOEL was 2 mg/kg/day. An UF of 100 applied to the NOEL; 10 X each for inter and intra species variability. Thus an RfD of 0.002 mg/kg/day was derived.

For chronic dietary risk assessments, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained** for a **total UF of 1000.**. [i.e.,10 for intra-species variation x 10 for inter-species variation x 10 for FQPA]: **Thus the revised RfD is: 0.0002 mg/kg/day.** The UF of 1000 is supported by the following factors:

(I) The concern for the potential of Naled to induce adverse effects in the functional development of a fetus based on the severity of the effects seen in the brain (50% decrease in cholinesterase activity) and the spinal cord (axonal degeneration) in hens given a single oral dose;

(ii) The primary effect (i.e., cholinesterase inhibition) was not well characterized, particularly in regard to adults and offsprings. There were no measurements of cholinesterase activity either in the adults or in the offspring in the developmental and reproduction studies. Even though the measurement of cholinesterase inhibition in these studies is not a requirement, measurement of this endpoint may have provided critical data needed for evaluation of sensitivity between adults and offsprings

(iii) There were no measurements of cholinesterase activity either in the adults or in the offspring in the developmental and reproduction studies or in the acute and subchronic neurotoxicity studies in rats.

(iv) The existing data gap for a 28/90-day study in hens in spite of severe neurotoxic effects seen in the acute delayed neurotoxicity study. Data from this study will assist in determining the need for a developmental neurotoxicity study in rats.